DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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Daniel R. Dwyer
Kleinfeld, Kaplan and Becker
1140 Nineteenth Street, N.W.
Washington, D.C. 20036-6601

Re: Docket No. 80N-0042
Comment No. CP8

Dear Mr. Dwyer:

Reference is made to your citizen petition dated August 21, 1998, filed as Comment No. CP8 under Docket No. 80N-0042 in FDA's Dockets Management Branch, regarding biological testing requirements for over-the-counter (OTC) anticaries drug products. The petition requests that the Food and Drug Administration (FDA) not accept an intra-oral remineralization test as a substitute for the animal caries reduction test required by 21 CFR § 355.70(a) to demonstrate the effectiveness of fluoride dentifrices without the consensus of the scientific community.

Your petition states that on September 27, 1996, FDA granted a citizen petition from Tom's of Maine (Tom's) to permit the use of an intra-oral remineralization test in humans for Tom's original formula dentifrice as a substitute for the currently required animal caries reduction test. The petition contends that this action indicates that FDA has concluded that the remineralization test is an acceptable substitute for the animal caries reduction test when there are significant questions as to whether the remineralization test is appropriate for this use. To support this position, the petition includes the report of three recognized experts in the field of dental caries who believe that the remineralization test is not as reliable as the animal caries reduction test in demonstrating fluoride ion availability in OTC dentifrices.

The petition further contends that although the anticaries final monograph permits alternative testing, the agency indicated that it would not consider such testing unless adequate data were submitted "in the form of a petition to amend the monograph" (60 FR 52474 at 52500). An amendment to the monograph would, thus, make any substitute testing proposals subject to notice-and-comment rulemaking. The Division of OTC Drug Products has reviewed your petition and has the following comments:

As your petition notes, the agency concluded in the preamble to the anticaries final monograph that differences in individual product formulations could greatly influence the effectiveness of fluoride dentifrices in preventing dental caries (60 FR 52474 at 52499).

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Because inactive ingredients can affect the bioavailability of fluoride during toothbrushing, the agency was concerned that newer formulations might reduce the availability of fluoride ions when these formulations are diluted in the mouth or exposed to reactions between dentifrice ingredients and salivary components (60 FR 52474 at 52500). The agency concluded that although *in vitro* tests may show positive results that are predictive of anticaries activity, a reduction in fluoride ion availability might not be detected by these tests and the product may not provide the expected level of effectiveness during actual use.

The agency further concluded that biological testing is necessary to ensure the effectiveness of anticaries drug products containing active fluoride ingredients. Because the animal caries reduction test directly measures the effectiveness of a fluoride dentifrice in an animal model *in vivo* after limited brushing, FDA concluded that this test gives a more complete assessment of tested formulations compared with the two *in vitro* tests (fluoride enamel uptake and enamel solubility reduction). Therefore, the use of both animal and human studies was required as a more complete assessment of anticaries effectiveness.

FDA further encouraged the development of additional testing procedures such as remineralization tests, but noted that sufficient data were not available to correlate these tests specifically with clinical studies that demonstrate the effectiveness of fluoride dentifrices (60 FR 52474 at 52500). FDA stated in the preamble that it would consider such tests as an option to the animal caries reduction test (i.e., to be included in the monograph) "if adequate data were submitted to the agency in the form of a petition to amend the monograph" (60 FR 52500). However, FDA stated in part 355.70(c) that any proposed modification or alternative testing procedures should be submitted as a petition containing data to support the modification or demonstrating that an alternative testing procedure provides results of equivalent accuracy.

Thus, these proposed substitute tests may be submitted as a petition to amend the monograph or they may be submitted as a petition to allow the use of a substitute test to demonstrate the anticaries effectiveness of a specific formulation. An example of the latter type of petition was the Tom's petition that you mentioned. The Tom's petition did not request amendment of the monograph and, therefore, was not subject to notice-and-comment rulemaking. In addition, although the agency recommended that modifications or substitute tests be generally accepted by the scientific community, this was not a requirement.

Tom's petitioned FDA in 1996 to accept the results of a completed test conducted in humans wearing an intra-oral appliance (IOA) with attached enamel chips as a substitute for the animal caries reduction test. Although the agency had initial concerns about the design and results of this test, the data were considered sufficient to accept the proposed study as an alternative to the animal caries model to demonstrate the effectiveness of Tom's original dentifrice formulation. Tom's requested that the results of this IOA model be accepted as evidence of the effectiveness of their other formulations. However, because these formulations contain different abrasives and flavorings, FDA is requiring that all of Tom's other formulations be tested individually. The agency also recommended that protocols for any further IOA tests be submitted for review prior to conducting the tests. Tom's submitted a new IOA protocol that was revised based on discussions with the agency.

The Tom's IOA study used a custom fabricated appliance containing 16 small pieces of enamel obtained from extracted human molars. Some of the enamel specimens were exposed to acid solutions to induce demineralization. Subjects wore the appliance for three 30-day periods during which either a negative control dentifrice (without fluoride), a positive control dentifrice (containing sodium monofluorophosphate), or the test formulation (Tom's Natural Toothpaste with fluoride) was used. Subjects wore the appliance continuously except during meals (when the appliance was placed in a 10-percent sucrose solution for 15 minutes) and while brushing their teeth. Subjects removed the appliance and brushed following breakfast, lunch, and at bedtime. The appliance was then replaced in the mouth and the assigned dentifrice was applied to the enamel samples with a cotton swab, where it remained for one minute prior to rinsing. The enamel samples (both untreated samples and those demineralized by acid exposure) were evaluated for hardness, acid resistance, fluoride and calcium content, and mineral density.

Your petition presents two major criticisms of the IOA model. The first is that the IOA model addresses demineralization but not remineralization. The second is that placement of the enamel blocks in the appliance and the use of a gauze covering do not adequately mimic realistic caries challenges.

In the Tom's study (described above), the demineralized samples were examined to determine their ability to remineralize and the untreated samples were examined to determine their ability to resist demineralization. Although gauze was not used in this study, the use of gauze in IOA studies enables the enamel blocks to retain plaque, subjecting the enamel to an exaggerated challenge. Because caries only forms in the mouth as a result of exposure to plaque, this facilitates the measurement of the activity of fluoride during a plaque challenge.

There is apparently some disagreement among the scientific community regarding the scope and capabilities of IOA models. For example, in a special issue of the Journal of Dental Research devoted to *in-situ* testing for dental caries (Workshop on Technological Advances in Intra-Oral Model Systems Used to Assess Cariogenicity, 71: April, 1992) the following statement was made regarding the acceptance of IOA testing:

> In 1989, the Council on Dental Therapeutics of the American Dental Association accepted a new, modified fluoride dentifrice based largely upon the data resulting from intra-oral models. This acceptance marked an important departure from the Council's past practice of accepting modified anticaries agents only when conventional clinical trials had demonstrated a statistically significant benefit. This approval thus resulted in the acknowledgment by the Council, as had been recognized by the scientific community, that intra-oral models could be used as a potential indicator of clinical efficacy.

It is also stated in this issue that additional guidelines would have to be established to define the specific role that IOA models could serve in the assessment of the effectiveness of anticaries agents and that further consideration would be required to establish the validity and reliability of these models.

As a result, interim guidelines were developed that require that IOA studies used for approval of product claims by the American Dental Association (ADA) be able to demonstrate statistically significant, dose-response differences in the effectiveness of products containing different concentrations of fluoride. According to Dr. Conrad Naleway, editor of the 1992 issue of the Journal of Dental Research mentioned above, the ADA will waive the animal caries reduction test if IOA data are sufficient to support caries reduction.

Another potential advantage of IOA studies is comparability to normal dentifrice use, whereas it can be difficult to extrapolate clinical effectiveness data from the results of rat caries studies. Because rats are superinfected with cariogenic bacteria and, unlike clinical subjects, swallow the fluoride toothpaste, it may be difficult to determine if the caries reduction is a result of the systemic action of fluoride rather than its action on the surface of the enamel in the oral cavity. Further, the use of a removable appliance containing multiple enamel specimens offers a number of important advantages. Most importantly, this method provides a sufficient number of specimens for several different analyses to be used, resulting in a comprehensive characterization of the remineralization process. Specifically, microradiography demonstrates the occurrence and extent of remineralization, fluoride uptake measures *in-situ* bioavailability of fluoride, and microhardness and acid-resistance testing measure the stability of remineralized enamel lesions. Multiple specimens also ensure that sufficient samples are available even if some are damaged during wearing or analysis.

As the authors of the report included in the petition point out, the animal caries reduction study has a long history of reliability in demonstrating the effectiveness of fluoride dentifrices and was included by FDA as a requirement of the OTC anticaries final monograph. However, as noted above, the agency also encourages the development of additional testing procedures and believes that a well-conducted IOA study is a measure of both remineralization and demineralization of tooth structure that can provide results which, when compared to the animal caries model, can provide results of equivalent accuracy.

At the time that the Tom's petition to accept an IOA study as a substitute for the animal caries reduction test was granted, FDA did not anticipate many similar requests. However, the receipt of three recent submissions requesting substitution of an IOA model for the animal caries test as well as your petition opposing these requests, indicates that there is some disagreement among the scientific community about whether IOA or animal caries studies provide sufficient evidence of both demineralization and remineralization. There is also disagreement as to whether the advantage of the IOA model, which uses human teeth, outweighs the claimed predictability and the experience of the animal model.

Because of this lack of consensus within the dental community regarding the respective tests and the apparent increased interest among manufacturers to rely on IOA tests in lieu of animal studies to demonstrate the effectiveness of new fluoride formulations, it is appropriate to address these issues in a public forum where experts can debate the usefulness and acceptability of alternate biological testing methods such as the IOA model.

However, as noted above, the anticaries final monograph allows for proposed modifications or substitute biological tests that are reviewed on an individual basis without the requirement for a notice-and-comment rulemaking. Further, the criticisms of the IOA model presented in the

petition are not sufficient to conclude that the use of this test as an alternative to the animal caries reduction test is unacceptable.

Accordingly, your petition is denied. Any comments or additional information should be submitted in triplicate, identified with the docket and comment numbers at the top of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852.

I hope this information will be helpful.

Sincerely yours,

for Dennis E. Baker
Associate Commissioner
for Regulatory Affairs